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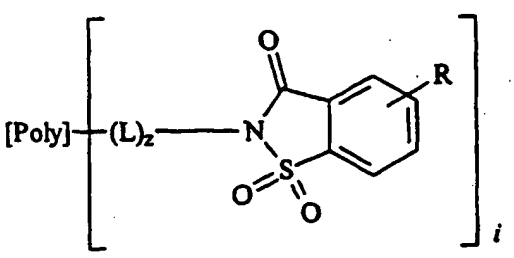

(I)

(57) Abstract: The present invention relates to enzyme inhibiting polymer conjugates, preferably a polymer conjugate having formula (I): wherein R is a unit which acts to attenuate the interaction of the saccharin inhibitor component with a target enzyme, L is a linking group; [Poly] is a polymeric unit, *i* indicates the number of said saccharin units which comprise said conjugate and has the value of from 1 to 100; z is 0 or 1, said polymer conjugates suitable for use in preventing skin irritation resulting from exposure of the skin to body fluids, *inter alia*, faces menstrual fluid. The conjugates of the present invention are useful in diapers, dressings, sanitary napkins, and the like.

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ENZYME INHIBITORS

FIELD OF THE INVENTION

The present invention relates to novel functional polymer conjugates which inhibit one or more proteolytic and/or lipolytic enzymes. The polymer conjugates described herein are suitable for use in any context wherein proteolytic and/or lipolytic enzyme inhibition is indicated, *inter alia*, treatment of diaper rash.

BACKGROUND OF THE INVENTION

Diaper rash is ubiquitous. It was once believed that contacting the skin with urine produced diaper rash, however, it is now understood that the irritation of tissue which manifests itself in "diaper rash" is primarily caused by endogenic proteolytic and/or lipolytic enzymes, *inter alia*, trypsin, chymotrypsin, elastase, pancreatic lipase, which comprise human feces. However, skin irritation is not limited to enzymes which comprise feces, for example, menstrual fluids may provide a source of enzymes which produce irritation.

Proteolytic and lipolytic enzyme inhibitors are known. An example of effective inhibitors are "suicide inhibitors" which irreversibly react with the active site of the target enzyme thereby destroying the enzyme's ability to function. Reversible enzyme inhibitors, although not permanently inactivating the target enzyme, are also considered sufficiently effective to inhibit the effects of unwanted enzyme exposure. One drawback of low molecular weight enzyme inhibitors is their propensity to be readily absorbed through skin tissue, thereby entering into human cells wherein normal cell catabolism can be interrupted.

There is a long felt need to provide a barrier against the pernicious enzymes which act to irritate human skin, especially enzymes which produce diaper rash.

SUMMARY OF THE INVENTION

The present invention meets the aforementioned needs in that it has been surprisingly discovered that proteolytic and/or lipolytic enzyme inhibitors can be effectively delivered to human skin wherein said inhibitors can function as a barrier to enzyme activity thereby preventing diaper rash. The enzyme inhibitors of the present invention are polymer conjugates which have an enzyme inhibitor component and a functionalized polymer component.

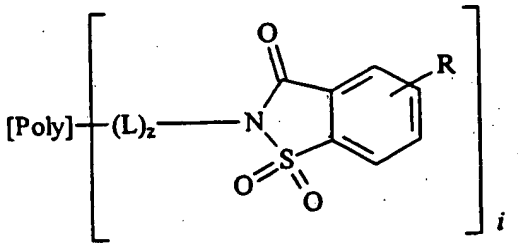
The enzyme inhibitor component comprises a heterocyclic ring template and an enzyme targeting unit. The functionalized polymer component comprises a moiety which acts as an anchoring template for one or more enzyme inhibitors while providing a means for delivering the conjugate molecule to human skin. The enzyme inhibitor component is optionally, but preferably,

linked to the functionalized polymer component by a linking group. As described herein below, preferably said linking units function by interacting with the enzyme, as a leaving group, *inter alia*, which can potentially unmask an electrophile in the enzyme active site which leads to effectively irreversibly inhibiting the target enzyme.

A first aspect of the present invention relates to an enzyme inhibiting polymer conjugate having the formula:

$$[Poly]—(L)_z—T$$

wherein T is a saccharin ring-comprising inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1; preferably a polymer conjugate having the formula:



wherein preferably a linking group, L, is directly bonded to the nitrogen atom of the heterocyclic ring.

In a preferred aspect of the present invention linking unit L also serves as a leaving group which facilitates irreversible binding to the target enzyme.

The present invention further relates to a process for preventing the formation of skin irritation which is due to the presence of proteolytic and/or lipolytic enzymes, said process comprises the step of contacting an effective amount of a polymer conjugate as described herein below to human skin.

These and other objects, features and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (° C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the prevention of pernicious and otherwise unwanted skin conditions, *inter alia*, rash, irritation, which is caused by the contact of proteolytic and/or lipolytic enzymes with skin. Among the conditions which the present invention seeks to ameliorate is diaper rash. The present invention achieves the desired result by applying to the skin by a

suitable means a sufficient amount of a polymer conjugate which inhibits the activity of one or more enzymes which are the cause of said unwanted skin condition.

The polymer conjugates of the present invention comprise a saccharin enzyme inhibitor component. The saccharin component is substituted by one or more units which activate or de-activate the enzyme inhibiting component towards one or more proteolytic or lipolytic enzymes. One or more saccharin enzyme inhibiting components may be present in the polymer conjugates of the present invention.

The conjugates of the present invention further comprise a functionalized polymer component which acts as an anchoring template for one or more enzyme inhibitors while providing a means for delivering the conjugate molecule to human skin. The functionalized polymer component is typically an amphiphilic polymer which is capable of being directly attached to the enzyme inhibitor component or of being attached thereto by a linking unit. The polymer component also provides the conjugate with a source of increased molecular weight which acts to inhibit the absorption of the enzyme inhibitor into skin tissue. The polymer component also acts to facilitate formulation of the enzyme inhibitor into carriers or facilitates deposition of the conjugate on to either skin or a substrate to which said conjugate is applied.

The conjugates of the present invention also optionally comprise a linking unit which serves to tether the enzyme inhibitor portion of the conjugate to the polymeric component. Although the polymer may be bonded directly to the enzyme inhibiting heterocycle, preferably a linking group is present to facilitate preparation and attachment of the polymer thereto. The linking group is preferably a unit which also has an interaction with the target enzyme or other enzymes which may be present, said interaction may increase selectivity for the target enzyme or aid in decreasing the affinity for a non-targeted enzyme. The linking group therefore serves a dual role; acting in a manner which modulates the specificity of the polymer conjugate while providing a means for linking the enzyme inhibitor portion to the polymer backbone. Another aspect of preferred linking groups is the capacity in certain instances of the linking groups to interact with the enzymes prior to the inhibitor portion of the polymer conjugate interacting with the target enzyme, for example, pre-orienting the inhibitor portion within the active site of the enzymes.

However, the linking unit may serve a purpose not related to the enzyme activity of the polymer conjugate. For example, the linking unit may serve to provide hydrogen bonding with the solvent affording increased compatibility of the inhibitor portion with the carrier.

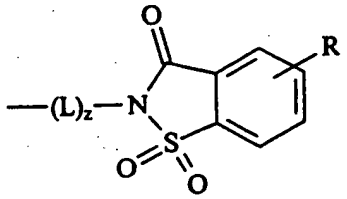
The polymer conjugates of the present invention are utilized in an effective amount. For the purposes of the present invention the term "effective amount" is defined herein as the amount

necessary to provide a reduction in enzyme activity in at least one inhibition assay. Preferred assays which are described herein are, *inter alia*, "Fecal Protease Inhibition Assay", "Skin Test of Inhibition of IL-1α Production". Suitable tests also include test which differentiate the specificity of said enzyme inhibitor, for example, which proteases are obstructed by said inhibitor.

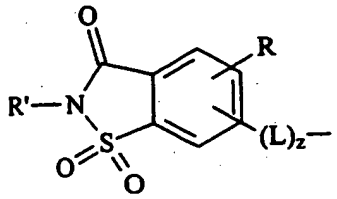
POLYMER CONJUGATES

Enzyme Inhibitor Component

The enzyme inhibitor component of the present invention comprises a saccharin moiety having the formula:



wherein the polymer component is linked to the nitrogen of the heterocyclic ring, or a saccharin moiety having the formula:



wherein the polymer component is linked to the benzene ring. In the first embodiment wherein the polymer is linked to the nitrogen, it is preferred that a linking group which also serves as a leaving group is present. In the latter embodiment, R' is preferably a unit which serves as a leaving group facilitating irreversible binding to the target enzyme. However, because the saccharin enzyme inhibitor component of the latter embodiment remains attached to the polymer component during and after interaction with the target enzyme, it is not a requirement that these inhibitors irreversibly bind to the target enzyme. For the purposes of the present invention the term "saccharin ring" is defined herein as a 1,2-benzisothiazol-3(2H)-one 1,1-dioxide ring or named alternatively, 2,3-dihydro-3-oxobenzisosulfonazole, and is used interchangeably with each of these chemical terms.

The enzyme inhibition component optionally comprises one or more enzyme differentiating units, R. R units serve to attenuate the interaction of the saccharin inhibitor component with the target enzyme. R units are:

a) hydrogen;

b) C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; preferably C_1-C_8 linear unsubstituted alkyl, *inter alia*, methyl and ethyl, especially when the enzyme inhibitor component comprises a benzoxazin-4-one moiety.

c) C_3-C_{18} substituted or unsubstituted, cycloalkyl; preferably C_6-C_{10} unsubstituted cycloalkyl;

d) C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl; preferably C_{10} and C_{15} branched alkenyl units derived from terpenes or other isoprene derived units;

e) C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl;

f) C_6-C_{18} substituted or unsubstituted aryl; preferably phenyl, biphenyl, naphthyl and the like;

g) C_2-C_{18} substituted or unsubstituted heterocyclic alkyl;

h) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

i) alkylenearyl having the formula:

$$—(R^1)_n—R^2$$

wherein R^1 is C_1-C_{12} linear or branched alkylene, C_2-C_{12} linear or branched alkenylene, or mixtures thereof; R^2 is C_6-C_{18} substituted or unsubstituted aryl, C_3-C_{18} heteroaryl, or mixtures thereof; n is from 1 to 16; a preferred alkylenearyl unit comprises substituted benzyl units;

j) an amino unit having the formula:

$$—(CH_2)_mN(R^3)_2$$

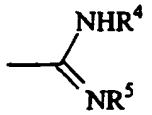
wherein each R^3 is independently hydrogen, C_1-C_{18} substituted or unsubstituted, linear, cyclic, or branched alkyl; m is from 0 to 10;

k) a quaternary ammonium unit having the formula:

$$—(CH_2)_m\overset{+}{N}(R^3)_3\ Y^-$$

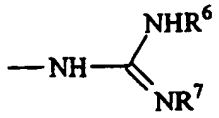
wherein each R^3 is independently hydrogen, C_1-C_{18} substituted or unsubstituted, linear, cyclic, or branched alkyl; Y is an anion of sufficient charge to provide electronic neutrality; m is from 0 to 10;

l) a unit having the formula:



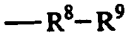
wherein R^4 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^5 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^4 and R^5 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms; preferred is amidine;

m) a unit having the formula:



wherein R^6 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^7 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^6 and R^7 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms; preferred are guanidine units and cyclic units, *inter alia*, imidazolinyl;

n) a unit having the formula:



wherein R^8 is:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

iii) $-C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

iv) $-C(X)R^{11}C(X)-$, wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

v) $-C(X)NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vi) $-C(X)NR^{10}R^{11}NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vii) $-NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

viii) $-NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

ix) $-NR^{10}C(X)R^{11}NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

x) $-NR^{10}R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xi) $-NR^{10}C(X)R^{11}C(X)O-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xii) $-OC(X)R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiii) $-NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiv) $-R^{11}NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xv) $-R^{11}NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xvi) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

xvii) -O-;

xviii) $-(R^{11})_tC(X)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xix) $-(R^{11})_tOC(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xx) $-(R^{11})_tC(O)O(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxi) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is from 1 to 4;

xxii) -S-;

xxiii) $-(R^{11})_tS(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxiv) $-(R^{11})_tS(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxv) $-(R^{11})_tSO_2(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxvi) or mixtures thereof;

R^9 is:

i) hydrogen;

ii) C_1-C_{18} substituted or unsubstituted, linear or branched alkyl;

iii) C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl

iv) C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl;

v) C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl;

vi) C_6-C_{18} substituted or unsubstituted aryl;

vii) C_2-C_{18} substituted or unsubstituted heterocyclic alkyl;

viii) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

ix) -OH;

x) $-SO_3M$;

xi) $-OSO_3M$;

xii) $-NO_2$;

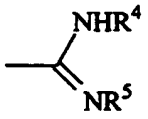
xiii) halogen selected from fluorine, chlorine, bromine, iodine, or mixtures thereof;

xiv) $-C(Hal)_3$, wherein each Hal is fluorine, chlorine, bromine, iodine, or mixtures thereof;

xv) $-COR^{14}$; wherein R^{14} is hydrogen, -OH, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, or mixtures thereof; $-N(R^{15})_2$, or mixtures thereof; each R^{15} is independently hydrogen, -OH, C_1-C_4 alkyl, or mixtures thereof;

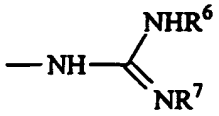
xvi) $-CH(OR^{14})_2$ wherein R^{14} is hydrogen, C_1-C_{12} alkyl, or two R^{14} units can be taken together to form a ring having from 3 to 5 carbon atoms; or mixtures thereof;

xvii) a unit having the formula:



wherein R^4 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^5 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^4 and R^5 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

xviii) a unit having the formula:



wherein R^6 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^7 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^6 and R^7 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

xix) -$NHOR^{16}$, wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; acyl having the formula -COR^{17}, wherein R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xx) a unit having the formula:

$$—CH=NOR^{16}$$

wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; C_7-C_{22} linear or branched alkylenearyl; acyl having the formula -COR^{17}, R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xxi) an amino unit having the formula:

$$—(CH_2)_mN(R^3)_2$$

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; m is from 0 to 10;

xxii) a quaternary ammonium unit having the formula:

$$—(CH_2)_m\overset{+}{N}(R^3)_3\ Y^-$$

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; Y is an anion of sufficient charge to provide electronic neutrality; m is from 0 to 10;

o) two R units on the same carbon atom can be taken together to form a carbonyl unit or carbonyl unit equivalent, *inter alia*, C=O, C=NH; and

p) mixtures thereof.

Preferred R units according to the present invention include:

a) hydrogen;

b) C_1-C_8 linear unsubstituted alkyl, for example, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, n-pentyl, isopentyl, n-hexyl, 2-methyl hexyl, 2-ethyl, hexyl. Methyl and ethyl are especially preferred when the enzyme inhibitor component comprises a benzoxazin-4-one moiety.

c) C_6-C_{10} unsubstituted cycloalkyl, for example cyclohexyl, 4-methylcyclohexyl, 4-isopropylcyclohexyl;

d) C_{10} and C_{15} branched alkenyl units derived from terpenes or other isoprene derived units, for example, 3,7-dimethyl-6-octen-1-yl; 3,7-dimethyl-2,6-octadien-1-yl; 3,7-dimethyl-1,6-octadien-3-yl;

f) phenyl, naphthyl, 4-methoxyphenyl, 4-nitrophenyl, 4-(C_1-C_4 alkyl)phenyl;

g) C_4-C_6 substituted or unsubstituted heterocyclic alkyl; non-limiting examples of which include 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolindinyl, 3-pyrrolidinyl, 2-piperazinyl, N-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, N-morpholinyl, and mixtures thereof;

h) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl; 2-pyrrolyl, 3-pyrrolyl;

i) alkylenearyl having the formula:

$$—CH_2—R^2$$

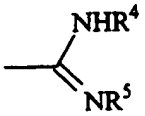
wherein R^2 phenyl, substituted phenyl, pyridinyl, substituted pyridinyl;

j) an amino unit having the formula:

$$—N(R^3)_2$$

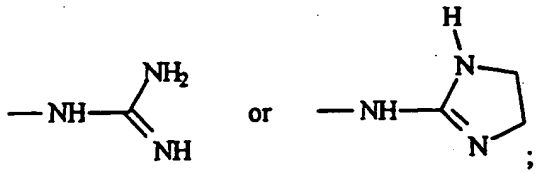
wherein each R^3 is independently hydrogen, methyl, ethyl, 2-hydroxyethyl, cyclopropyl; for example, methylamino, dimethylamino, ethylamino, diethylamino, dicyclopropyl;

l) a unit having the formula:



wherein R^4 and R^5 are each hydrogen, R^4 and R^5 is taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms; preferably amidine, 2-pyridinyl, pyrimidinyl, imidazolyl;

m) a unit having the formula:



n) a unit having the formula:

$$—R^8—R^9$$

wherein R^8 is:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

xvi) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

xvii) -O-;

xxi) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is from 1 to 4;

xxii) -S-;

xxvi) or mixtures thereof;

R^9 is:

i) methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl; preferably methyl when R^8 is –O-;

ii) cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 2,5-dimethylcyclopentyl;

v) phenyl, 4-methoxyphenyl, 4-nitrophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-aminobenzyl, 4-guanidiobenzyl;

vi) N-aziridinyl, 2-pyrrolindinyl, 3-pyrrolidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl;

viii) -OH, when the index p is from 1 to 4, preferably when p is 1;

ix) $-SO_3M$ when the index p is from 1 to 4, preferably when p is 1;

x) $-OSO_3M$ when the index p is from 2 to 4, preferably when p is 2;

xi) $-NO_2$;

xii) chlorine, bromine, or mixtures thereof; more preferably chlorine;

xiii) $-CF_3$;

xiv) $-CO_2R^{14}$; wherein R^{14} is hydrogen, $-NH_2$, $-N(CH_3)_2$, or mixtures thereof;

xvii) $-NHOR^{16}$, wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; acyl having the formula $-COR^{17}$, wherein R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xviii) a unit having the formula:

$$—CH=NOR^{16}$$

wherein R^{16} is hydrogen, or methyl; and

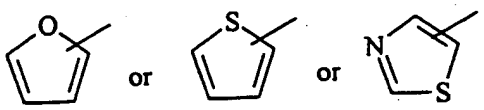
p) mixtures thereof.

For the purposes of the present invention the term "substituted or unsubstituted, linear or branched" is defined herein as the following. Alkyl chains which comprise, for example, a C_1-C_{18} alkyl unit will have any combination of carbon atoms arranged in linear form or with one or more branching chains provided the total number of carbons is from 1 to 18 carbon atoms. By the term "substituted" is meant any unit which suitably replaces a hydrogen atom of a linear or branched chain, non-limiting examples of which include halogen, hydroxyl, nitro, amino, cyano, $-CO_2M$, $-SO_3M$, $-OSO_3M$, wherein M is a water soluble cation. For alkenyl units, one or more double bonds may be present and said bonds may be conjugated or non-conjugated. Alkenyl units also include allenes. For aryl units, substituents may comprise alkyl units as will as halogen, etc.

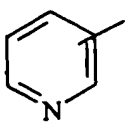
R units can take any form which modulates the enzyme inhibition properties of the T unit. For example, R units under (i) above are alkylenearyl having the formula:

$$—(R^1)_n—R^2$$

wherein R^1 is C_1-C_{12} linear or branched alkylene, C_2-C_{12} linear or branched alkenylene, or mixtures thereof; R^2 C_6-C_{18} substituted or unsubstituted aryl, C_3-C_{18} heteroaryl, or mixtures thereof; n is from 1 to 16. Non-limiting examples of suitable heteroaryl units are 5-member rings which have the formula:



or a 6-member ring having the formula:



wherein said unit can be attached at any carbon atom.

Non-limiting examples of heterocyclic units suitable for use in the present invention include thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, triazolyl, tetrazolyl, benzothiazolyl, benzofuryl, indolyl, indenyl, azulenyl, fluorenyl, oxazolyl, isoxazolyl, isotriazolyl, imidazolyl, pyraxolyl, oxadiazolyl, indolizinyl, indolyl, isoindolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, and mixtures. The heterocyclic ring can be substituted, for example, 2-pyridinecarboxylic acid (picolinyl) The heterocyclic ring can be incorporated in any manner, for example, as a 2-pyridinyl unit (picolyl) or bonded to the heteroatom, for example, N-aziridinyl, N-pyrrolidinyl.

Conjugates of the present invention which are salts or salt-forming compounds will preferably have counter ions which facilitate delivery or formulation. For example, preferred cations include sodium, potassium, lithium, ammonium, alkylammonium, and the like. Preferred anions include halogen, preferably chlorine, methylsulfate, and the like. However, di-basic acids, *inter alia*, oxalic, fumaric, succinic, may be used to form deliverable salts as well.

Polymeric Component

The polymeric component of the present invention comprises units which provide the herein described conjugates with one or more properties which facilitate the delivery of the enzyme inhibitor to the required substrate.

The polymeric unit or the present invention, represented by [Poly]- can be bonded directly to the enzyme inhibiting component or can be attached by way of a linking unit.

The polymeric materials of the present invention comprise:

i) a polyalkyleneoxy unit having the formula:

$$R^{19}(OR^{18})_x—$$

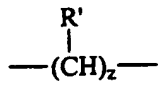
wherein R^{18} is C_2-C_{12} linear alkylene, C_3-C_{12} branched alkylene, phenylene, C_7-C_{12} alkylenearylene, and mixtures thereof; R^{19} is hydrogen, C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl; C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl; C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl; C_6-C_{18} substituted or unsubstituted aryl; and mixtures thereof. The index x has the value of from about 10 to about 500. The polyalkyleneoxy unit may be a homopolymer, (e.g., all ethyleneoxy units), co-polymer (e.g., a mixture of ethyleneoxy and propyleneoxy units), or a block co-polymer. The average molecular weight of a polyalkyleneoxy polymeric unit according to the present invention is from about 400 daltons, preferably from about 1500 daltons, more preferably from about 3400 daltons to about 35,000 daltons, preferably to about 20,000 daltons, more preferably to about 10,000 daltons, most preferably to about 8000 daltons.

ii) a co-polymeric polyalkyleneoxy unit having the formula:

$$R^{19}(OR^{18})_x(OR^{20})_y-$$

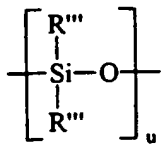
wherein R^{18} is C_2-C_{12} linear alkylene, C_3-C_{12} branched alkylene, phenylene, C_7-C_{12} alkylenearylene, and mixtures thereof; R^{19} is hydrogen, C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl; C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl; C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl; C_6-C_{18} substituted or unsubstituted aryl; and mixtures thereof; R^{20} is a unit selected from:

a) a unit having the formula:



wherein R' is hydrogen, methyl, allyl, hydroxyl, a linking group L which links an enzyme inhibiting component to the polymeric component as described herein below; $-(CH_2)_z$-J wherein J is selected from the group consisting of hydrogen, $-CO_2M$, $-OSO_3M$, $-SO_3M$, $-OPO_3M$, $-PO_3M$, $-N(R'')_2$, $-C(O)N(R'')_2$, $-NHC(=NH)NH_2$, $-CCl_3$, $-CF_3$, and mixtures thereof, wherein R'' is hydrogen, C_1-C_4 alkyl, or mixtures thereof; M is a water soluble cation, preferably ammonium, sodium, or potassium; z is from 1 to 12, z' is from 0 to 6; z + z' is preferably less than 7. The index x has the value of from about 10 to about 500. The index y has the value of from about 10 to about 100.

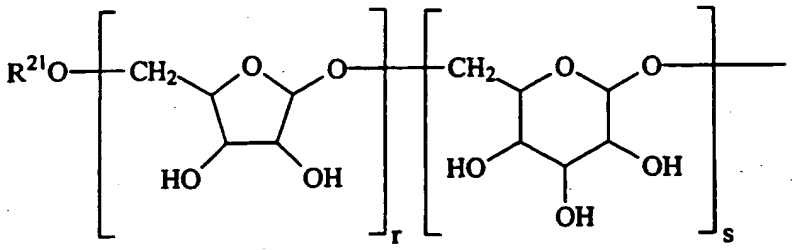
b) a unit having the formula:



wherein R''' is C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, a continuation of the chain by branching, or mixtures or mixtures; u has the value of from about 3 to 100. The molecular weight of a polymeric component which comprises a co-polymeric polyalkyleneoxy unit is such that the desired viscosity and solubility of the entire molecule fits the needs of the formulator. For example, units from (a) which comprise one or more linking units to enzyme inhibiting components may incorporate one or more hydrophilic units into the chain to increase the

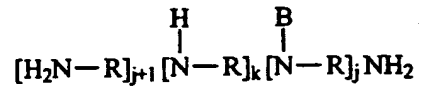
solubility of the final conjugate polymer. However, any of the polymers described herein can be random co-polymers or block co-polymers.

iii) a polysaccharide unit having the formula:



wherein R^{21} is hydrogen, C_1-C_4 alkyl, and mixtures thereof; the indices r and s are each independently from 0 to 100. The polysaccharide units of the present invention can be any mixture of 5 and 6-member ring sugar units, *inter alia*, sucrose, glucose, mannose, fructose.

iii) a polyamine unit having the formula:



R is C_2-C_{12} linear alkylene, C_3-C_{12} branched alkylene, and mixtures thereof; preferably R is ethylene, 1,3-propylene, and 1,6-hexylene, more preferred is ethylene. The indices j and k are such that the molecular weight of said polyamines does not exceed about 30,000 daltons. For example, for an entirely linear polyethyleneimine having a molecular weight of about 600 daltons, the index k is equal to 13 and j is equal to 0. For an entirely branched polyethyleneimine having a molecular weight of approximately 600 daltons, the index j is equal to 7. (This combination of indices results in a material having an average molecular weight of about 646 daltons, which, for the purposes of the present invention is a low molecular weight polyalkyleneimine.) The enzyme inhibiting component may be linked or directly bonded to any of the backbone nitrogen units.

The polymeric component of the present invention may be a mixture of one or more of the polymeric units described herein above. In addition, the formulator may attach to the polymeric component of the polymer conjugate as many linking units as necessary to deliver the required number of enzyme inhibiting components. One preferred permutation of admixtures of different components are star polymers as described in "Synthesis of Star-Shaped Poly(ethylene oxide)", Y. Gnanou, et al., *Makromolecular Chemistry*, Vol. 189 (1988) pp. 2885-2892, U.S. 5,648,506 Desai et al., issued July 15, 1997, each of which is incorporated herein by reference.

The preferred polymer or copolymer unit [Poly] of the present invention are polyalkyleneoxy unit having the formula:

$$R^{19}(OR^{18})_x—$$

and co-polymeric polyalkyleneoxy units having the formula:

$$R^{19}(OR^{18})_x(OR^{20})_y—$$

wherein R^{19} is preferably methyl for conjugates which comprise one enzyme inhibitor component, R^{19} is preferably hydroxyethyl for conjugates comprising two enzyme inhibitor components. For the latter, the preferred [Poly] units have the formulae:

$$—OCH_2CH_2(OR^{18})_x— \quad \text{and} \quad —OCH_2CH_2(OR^{18})_x(OR^{20})_y—$$

R^{18} is preferably ethylene and R^{20} is preferably 2-propylene and when R^{18}, OR^{19}, and OR^{20} are taken together the [Poly] unit has a molecular weight of from about 500 daltons, preferably from about 1000 daltons, more preferably from about 2000 daltons, most preferably from about 3000 daltons to about 10,000 daltons, preferably to about 8,000 daltons, more preferably to about 7500 daltons. Preferred

$$R^{19}(OR^{18})_x(OR^{20})_y—$$

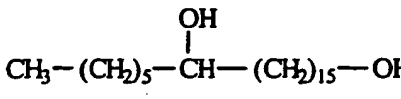
units are copolymer having random polymer units, for example, using EO for ethyleneoxy and PO for propyleneoxy, units having a formula:

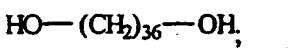
$$CH_3(EO)_{x'}(PO)_{y'}(EO)_{x''}(PO)_{y''}(EO)_{x'''}(PO)_{y'''}—$$

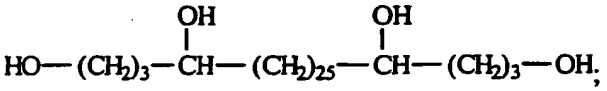
wherein $x' + x'' + x''' + y' + y'' + y'''$ represent a copolymer having a molecular weight of from about 500 daltons, preferably from about 1000 daltons, more preferably from about 2000 daltons, most preferably from about 3000 daltons to about 10,000 daltons, preferably to about 8,000 daltons, more preferably to about 7500 daltons.

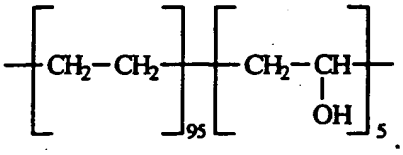
Non-limiting examples of suitable polyalkyleneoxy polymers for use in the present invention include polyethyleneglycol having an average molecular weight of 1500 daltons (PEG1500), 4000 daltons (PEG 4000), polyethyleneglycol having an average molecular weight of 5000 daltons (PEG 5000), polyethyleneglycol methyl ether having an average molecular weight of 1500 daltons (MPEG 1500), polyethyleneglycol methyl ether having an average molecular weight of 4000 daltons (MPEG 4000), polyethyleneglycol methyl ether having an average molecular weigh of 5000 daltons (MPEG 5000), block co-polymers of polyethylene glycol and polypropylene glycol (EO/PO co-polymers, wherein said PO unit can be 1,2-propylene, 1,3-

propylene, or mixtures thereof), for example Pluronics® available ex BASF. Also preferred are EO/PO/EO and PO/EO/PO co-polymers. One important embodiment of the present invention relates to conjugates which comprise multiple enzyme inhibitor components. This can be done by the formulator to increase the relative amount of inhibitor on a per weight basis of conjugate or to deliver multiple inhibitors per conjugate. The following are non-limiting examples of polyhydroxy units which are suitable for this embodiment.

a) 

b) 

c) 

d) 

Linking Units

The enzyme inhibiting polymer conjugates of the present invention optionally, but preferably, comprise one or more linking units, L. When the polymer component is bonded to more than one enzyme inhibiting units, the conjugate may comprise more than one linking unit. In addition, more than one type of linking unit may be present. For example, one type of linking unit may be convenient for one particular inhibitor component whereas a second unit is more compatible with a second type of heterocyclic enzyme inhibiting unit.

The linking units of the present invention may comprise any units capable of linking the enzyme inhibitor component to the polymer backbone. If the backbone is formed by random co-polymerization, the linking unit may be included. The linking group may be attached via "grafting" to the polymer backbone. Units which may conveniently serve as linking units are amino acids which have a carboxyl end and an amine end and which are capable of easy assembly into polymeric units (peptides). One or more amino acids taken together are a preferred means for linking the polymer unit and the enzyme inhibitor unit.

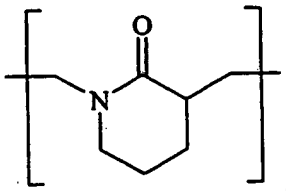
Preferred linking units of the present invention have the formula:

$$—(R^{11})_h\{(X)_j[C(X)]_k(X)_j(R^{11})_h(X)_j[C(X)]_k(X)_j\}_f(R^{11})_h—$$

wherein the unit having the formula:

$$—\{(X)_j[C(X)]_k(X)_j(R^{11})_h(X)_j[C(X)]_k(X)_j\}—$$

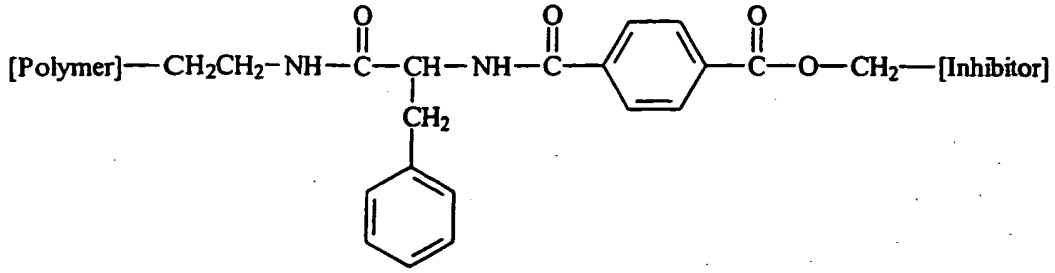
is preferably a repeatable unit, *inter alia*, amino acid, di-acid, wherein R^{11} is C_1-C_{12} substituted or unsubstituted alkylene; C_2-C_{12} substituted or unsubstituted alkenylene; C_3-C_{12} cycloalkylene; substituted or unsubstituted aromatic; *inter alia*, 1,2-phenylene, 5-sulfo-1,3-phenylene, 1,4-phenylene; substituted or unsubstituted heterocyclic, non-limiting examples of which include benzimidazole, benzimidazolone, pyridine, piperazine, pyrroline, imidazoline, imidazole, morpholine, oxazole, tetrazole, 1*H*-indenedione, oxazoline, quinoline, isoquinoline, thiazine, thiazole, benzothiophene, all of which can be linked either through a carbon atom or a heteroatom. The R^{11} units can be substituted or unsubstituted with any of the herein above defined $-R^8R^9$ units. X is oxygen, sulfur, NR^{10} wherein R^{10} is hydrogen, C_1-C_4 alkyl, phenyl, or R^{10} can be taken as part of a ring bonded to another moiety in the linking group, for example, a propylene unit forming a ring between the nitrogen and R^{11} as in the formula:



The indices h, j, and k are each independently 0 or 1. As indicated herein above, amino acids are a suitable and a preferred class of linking units, either alone, in combination with other amino acids, or other R^{11} units. The index f has the value from 0 to 10. An example of a linking unit comprising a repeatable unit (amino acid) wherein the index f greater than 1 is a linking unit having the general formula:

$$—(R^{11})_h\{NHCH(CH_3)C(O)\}\{NHCH_2C(O)\}(R^{11})_h—$$

wherein a first repeatable unit is an alanine residue and a second repeatable unit is a glycine residue. However, depending upon the value of the index f, any combination of repeatable units can be taken together to form a linking unit, for example, a linking unit having the formula:



The preferred linking units of the present invention comprise one or more units selected from the group consisting of:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

iii) $-C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

iv) $-C(X)R^{11}C(X)-$, wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

v) $-C(X)NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vi) $-C(X)NR^{10}R^{11}NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vii) $-NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

viii) $-NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

ix) $-NR^{10}C(X)R^{11}NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

x) $-NR^{10}R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xi) $-NR^{10}C(X)R^{11}C(X)O-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xii) $-OC(X)R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiii) $-NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiv) $-R^{11}NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xv) $-R^{11}NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xvi) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

xvii) -O-;

xviii) $-(R^{11})_tC(X)(R^{11})_t-$; wherein t is 0 or 1; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xix) $-(R^{11})_tOC(O)(R^{11})_t-$; wherein t is 0 or 1;

xx) $-(R^{11})_tC(O)O(R^{11})_t-$; wherein t is 0 or 1;

xxi) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is 1 or 2;

xxii) -S-;

xxiii) $-(R^{11})_tS(R^{11})_t-$; wherein t is 0 or 1;

xxiv) $-(R^{11})_tS(O)(R^{11})_t-$; wherein t is 0 or 1;

xxv) $-(R^{11})_tSO_2(R^{11})_t-$; wherein t is 0 or 1;

xxvi) or mixtures thereof.

More preferred L units according to the present invention include:

i) -C(O)-;

ii) -C(O)NH-;

iii) -C(O)R^{11}C(O)-, wherein R^{11} is methylene, ethylene, propylene, butylene, or mixtures thereof;

iv) -C(O)NHC(O)-;

v) -C(O)NHR^{11}NHC(O)- wherein R^{11} is methylene, ethylene, propylene, butylene, or mixtures thereof;

vi) -NHC(O)-;

vii) -NHC(O)NH-;

viii) -C(O)R^{11}NH-, R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof;

ix) -NHR^{11}C(O) -, R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof;

x) -NH-;

xi) -O-;

xii) -R^{11}OC(O)R^{11}-; wherein R^{11} is methylene, ethylene, propylene, butylene, or mixtures thereof;

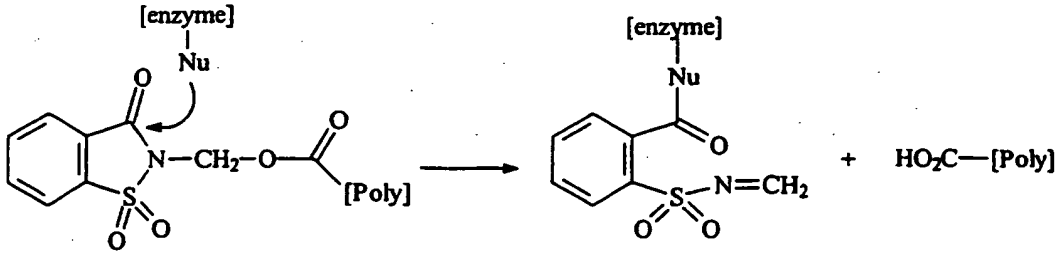
xiii) -R^{11}C(O) OR^{11}-; wherein R^{11} is methylene, ethylene, propylene, butylenes, or mixtures thereof;

xiv) or mixtures thereof.

The following are non-limiting examples of polymer conjugates according to the present invention.

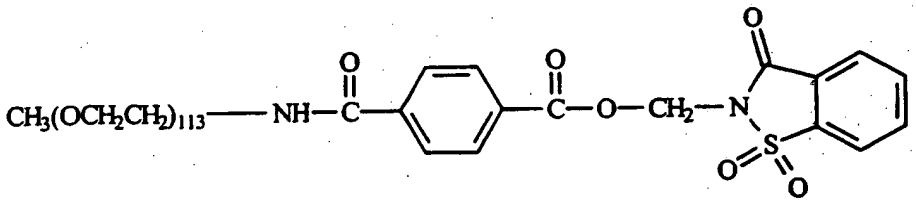
Preferred enzyme inhibiting units are derivatives of N-hydroxymethylsaccharin.

Without wishing to be limited by theory, the following is a proposed mechanism for the first step in the reaction between the polymer conjugates of the present invention and a target enzyme. In the example below an L unit serves as a leaving group which remains attached to the polymer component after the saccharin inhibitor component begins a series of reactions leading to irreversible binding to a target enzyme.

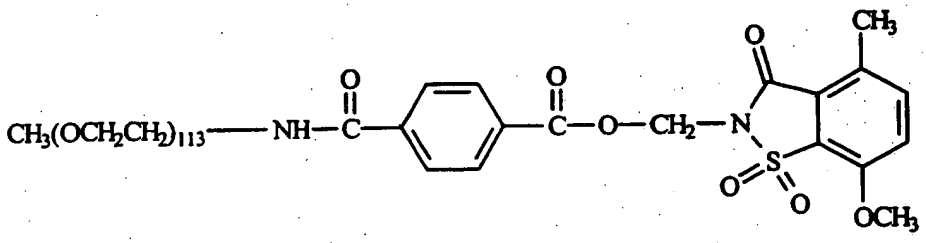


For the purposes of the examples of the present invention, PEG 5000 is used to represent methoxy capped polyethylene glycol homopolymer having an average molecular weight of about 5000 daltons.

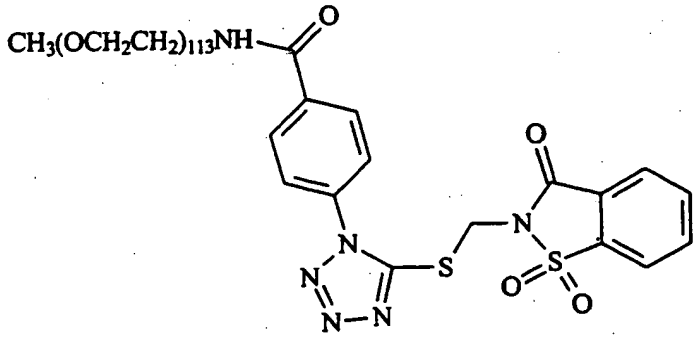
A preferred polymer conjugate, having the approximate IUPAC name N-(PEG 5000)-terephthalamic acid 1,1,3-trioxo-1,3-dihydro-1λ^6-benzo[*d*]isothiazol-2-ylmethyl ester, comprises an N-methylenesaccharin enzyme inhibiting component linked by a (xi) linking unit, -$NR^{10}C(X)R^{11}C(X)O$-, wherein R^{10} is hydrogen; R^{11} is unsubstituted phenylene; each X is oxygen; to a polyethyleneglycol polymer component having an average molecular weight of about 5000 daltons, said polymer conjugate having the formula:



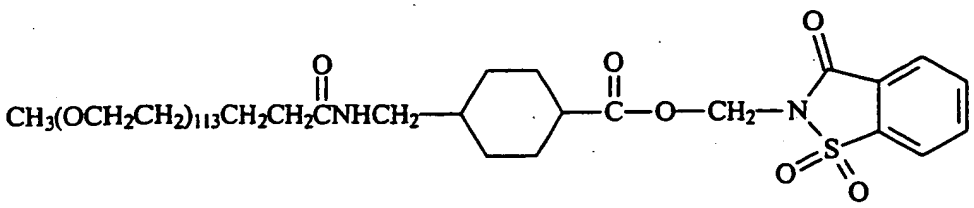
Another preferred polymer conjugate exemplifying a preferred R unit and which comprises the same linking unit and polymer component has the formula:



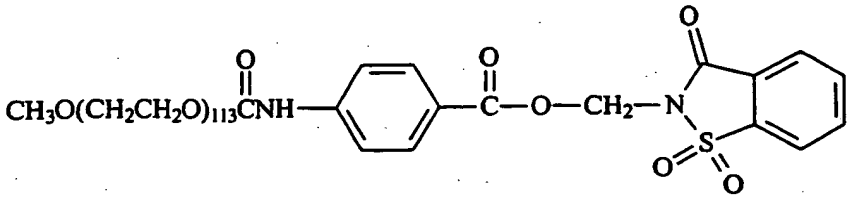
Another preferred polymer conjugate, having the approximate IUPAC name PEG 5000-carbamic acid 4-[5-(1,1,3-trioxo-1,3-dihydro-1λ^6-benzo[*d*]isothiazol-2-ylmethylsulfanyl)-tetrazol-1-yl]-phenyl ester, comprises a phenyl moiety and tetrazole moiety as the R^{11} unit, said polymer conjugate having the formula:



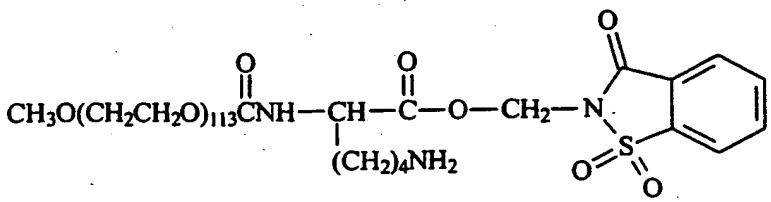
Another preferred polymer conjugate, having the approximate IUPAC name N-(PEG 5000 propanoyl)-tranexamic acid 1,1,3-trioxo-1,3-dihydro-1λ^6-benzo[*d*]isothiazol-2-ylmethyl ester, comprises a cyclohexylene and methylene moiety combination as the R^{11} unit, said polymer conjugate having the formula:



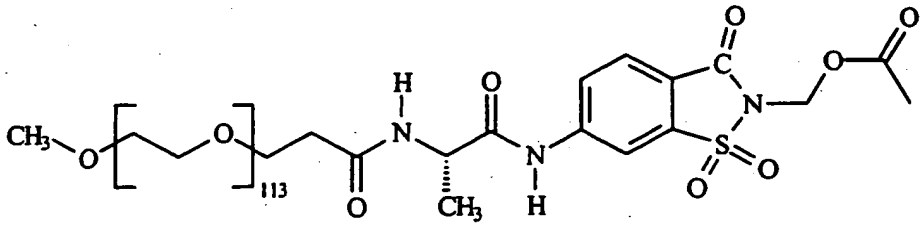
The following is a further example of a polymer conjugate according to the present invention which comprises a phenylene R^{11} unit:



The following is an example of a polymer conjugate according to the present invention which comprises an amino acid R^{11} unit:



The following is a further preferred polymer conjugate according to the present invention.



The following are non-limiting preparations of polymer conjugates according to the present invention.

EXAMPLE 1

Preparation of N-(PEG 5000)-terephthalamic acid 1,1,3-trioxo-1,3-dihydro-1λ^6-benzo[*d*]isothiazol-2-ylmethyl ester

PEG 5000 amine (0.5g, 0.1mmol) is combined with terephthalic acid (0.083 g, 0.5 mmol) and hydroxybenzotriazole hydrate (0.069 g, 0.5 mmol) in DMF (6 mL). To the stirred mixture is added dicyclohexylcarbodiimide (0.103 g, 0.5 mmol) and the reaction is allowed to stir for 18 hr. The resulting solid is removed by filtration and the filtrate diluted with ether. The resulting precipitate is collected by filtration to yield mono-PEG amido terephthalate.

The mono-PEG 5000 hemiamide from above (0.27 g, 0.05 mmol) is combined with N-bromomethyl saccharin (0.14 g, 0.5 mmol) in acetonitrile (10 mL). Triethylamine (0.11 g, 1 mmol) is added and the reaction gently heated to 40 °C for 2 hours then stirred at room temperature for 18 hours. The reaction solution is diluted with ether and the resulting solid collected by filtration. Recrystallization from ethanol yields the desired terephthalate amide-ester which is used without further purification.

EXAMPLE 2

Preparation of 5000-carbamic acid 4-[5-(1,1,3-trioxo-1,3-dihydro-1λ^6-benzo[*d*]isothiazol-2-ylmethylsulfanyl)-tetrazol-1-yl]-phenyl ester

1-(4-Hydroxyphenyl)-1*H*-tetrazole-5-thiol (0.15 g, 0.8 mmol), N-bromomethyl saccharin (0.2g, 0.72 mmol) and acetonitrile (6 mL) are combined and triethylamine (0.82 g, 0.8 mmol) is added and the reaction is allowed to stir for 18 hours. The solvent is removed under reduced pressure, the residue partitioned between ethyl acetate and water, and the organic phase concentrated to afford the saccharin tetrazole condensation product.

The product obtained from the preceding step (0.34 g, 0.85 mmol), triethylamine (0.09 g, 0.85 mmol) are combined in methylene chloride (6 mL). Mono-methoxy PEG 5000 isocyanate (1.0 g, 0.2 mmol) is dissolved in methylene chloride and added dropwise to the reaction solution. The reaction is stirred 18 hours after which time cold ether is added and the resulting precipitate is collected by filtration. Recrystallization from ethanol affords the desired saccharin polymer conjugate.

EXAMPLE 3

Preparation of N-(PEG 5000 propanoyl)-tranexamic acid 1,1,3-trioxo-1,3-dihydro-1λ^6-benzo[*d*]isothiazol-2-ylmethyl ester

N-bromomethyl saccharin (0.28 g, 1 mmol), N-Boc-tranexamic acid (0.26 g, 1 mmol) and acetonitrile (6 mL) are combined in a reaction vessel and DMF (1 mL) and triethylamine (0.15 mL) are added and the reaction is allowed to stir for 18 hours. The solvent is removed under reduced pressure, the residue partitioned between ethyl acetate and water, and the organic phase concentrated to afford the saccharin tranexamic acid condensation product.

The condensate from the preceding step is charged to a 25% solution of trifluoroacetic acid in methylene chloride (5 mL) and is stirred for 2 hours. The solvent is removed under reduced pressure and the resulting oil digested in and HCl/ether solution to afford the de-protected condensation product.

The de-protected condensation product as the HCl salt (0.035 g, 0.1mmol), PEG 5000 propionic acid (1 g, 0.2 mmol) and DMF (5 mL) are combined in a reaction vessel together with triethylamine (0.015 mL, 0,011g, 0.11 mmol). Dicyclohexylcarbodiimide (0.021 g, 0.1 mmol) is added. The reaction is stirred 18 hours after which time cold ether is added and the resulting precipitate is collected by filtration. Recrystallization from ethanol affords the desired saccharin polymer conjugate.

The polymer conjugates of the present invention are effective in treating and/or preventing one or more skin conditions, including irritation, resulting from the contact of enzymes with skin, *inter alia*, diaper rash. One effective means for delivering the stable conjugates to skin is via an article of manufacture, preferably an "absorbent article". Non-limiting examples of absorbent articles include sanitary napkins, panty liners, diapers, incontinence briefs, training briefs.

Typically the polymer conjugates of the present invention are formulated into a skin-compatible carrier which serves to solublized the conjugate in addition to providing a vehicle for uniform delivery of the enzyme inhibitor to the skin surface. The formulator of articles of manufacture which employ the enzyme inhibiting conjugates of the present invention will recognize the vehicle may take any form, *inter alia*, aqueous, non-aqueous, dry powder.

The amount of polymer conjugate which is present in the formulation depends upon the embodiment chosen by the formulator. In some instances, the polymer component of the conjugate itself may have properties which allow for the direct application of the conjugate without the need for a vehicle. However, when incorporated as part of a composition, the conjugate will comprise from about 0.01%, preferably from about 1% to about 20%, preferably to about 10% by weight, of the delivery vehicle.

The following are non-limiting examples of assays which may be used to determine the effective levels of the polymer conjugates of the present invention.

Fecal Protease Inhibition Assay

By way of illustration, to determine the activity of fecal protease inhibiting compounds, the compounds of the present invention may be tested in a standard enzyme assay for protease activity, as follows:

Infant feces are collected in a manner to keep them free from urine contamination and mixed with water to obtain a weight by weight (w/w) mixture (e.g., 1:4 w/w). This mixture is

then mixed thoroughly to obtain a homogeneous suspension by homogenization or sonication. The feces are then diluted with a reaction buffer, described below, to obtain a fecal concentration which, when added to a protease substrate, hydrolyzes the substrate over a 5 to 60 minute period. Using such a method, for example, fecal trypsin activity may be determined at pH 8.2 in a 50 nM Tris-HCl buffer with 20 mM $CaCl_2$, containing 0.3 mM of the composition to be tested; fecal chymotrypsin activity at pH 7.6 in a 50 mM Tris-HCl buffer with 20 mM $CaCl_2$, containing 0.05 mM of the composition to be tested; and fecal leucine aminopeptidase activity at pH 7.2 in 50 mM sodium phosphate containing the composition to be tested. To test the efficacy of the compositions, several different concentrations of each putative inhibitory composition are added to duplicate feces-containing reaction buffers, and the inhibition of the enzyme activity is measured. Compounds having an IC_{50} of 100 μM or less are preferred compounds of the invention. More preferred are compounds having an IC_{50} to IC_{90}, and most preferably an IC_{80} to IC_{90}, of 100 μM or less.

In Vitro Skin Test for Inhibition of IL-1α Production

An *in vitro* method to determine the efficacy of the compounds of the present invention in preventing the proinflammatory response of the skin to feces and fecal enzymes may be performed as follows:

Human keratinocytes are obtained from epidermal tissue and cultured in serum-free medium in plastic culture vessels containing a nylon mesh surface for a period of time until they are confluent. The mesh surface is then raised to the liquid air interface in order to promote differentiation and formation of multilayered organized layers analogous to those found *in vivo*, including a well defined stratum corneum barrier. Any cell culture system that promotes the growth and differentiation of keratinocytes, as described, may be employed. A commercially available cell culture system suitable for use is Epiderm® (MatTek Corporation).

Infant feces are collected in a manner to keep them free of urine contamination and diluted with phosphate-buffered saline (PBS) (pH 7.2 - 7.4). The mixture is then mixed thoroughly to obtain a homogenous suspension by homogenization or sonication. To assay for IL-1α production due to fecal enzyme activity, an aliquot of the homogenate is diluted with PBS and added to the surface of a control culture in a culture vessel. To assay for inhibition of IL-1α production due to protease activity, a predetermined quantity of a putative inhibitor (compound) is added to an otherwise identical diluted aliquot of the homogenate prior to adding it to the surface of a test culture. The cultures are allowed to incubate in a controlled atmosphere. At selected times, the control cultures and inhibitor-treated test cultures, and the underlying culture media are harvested. The culture media are assayed for the presence of IL-1α by known

methods. For example, a suitable assay for IL-1α is an enzyme-linked immunoabsorbent method commercially available as Quantikine® from R&D Systems.

The percent reduction in IL-1α production due to the presence of the compound (inhibitor) is calculated as follows:

$$\% \text{ Reduction} = \left[\frac{(\text{IL-1}_\alpha \text{ from control culture}) - (\text{IL-1}_\alpha \text{ from test culture})}{(\text{IL-1}_\alpha \text{ from control culture})} \right] \times 100$$

The polymer conjugates of the present invention are effective in treating and/or preventing one or more skin conditions, including irritation, resulting from the contact of enzymes with skin, *inter alia*, diaper rash. One effective means for delivering the stable conjugates to skin is via an article of manufacture, preferably an "absorbent article". Non-limiting examples of absorbent articles include sanitary napkins, panty liners, diapers, incontinence briefs, training briefs.

Adjunct biologically active ingredients

The formulator can add to the compositions of the present invention one or more "adjunct biologically active ingredients" to adjust the properties of the composition or to serve as an aid, *inter alia*, to healing of skin, booster to enzyme inhibition. When present the adjunct biologically active ingredients comprise from about 0.01%, preferably from about 0.05%, more preferably from about 0.1% to about 5%, preferably to about 2%, more preferably to about 1% by weight, of said composition.

A non-limiting example of a biologically active adjunct ingredient is hexamidine, 4,4'-[1,6-hexanediylbis(oxy)]bisbenzenecarboximidamide. Hexamidine is preferred as an adjunct to the polymer conjugates of the present invention. Without being limited by theory or application, hexamidine has multiple properties ascribed thereto, *inter alia*, as a topical antiseptic: *Bordeaux Med.*, M. J. Fénelon, **3**, 867 (1970); as an antibacterial: *J. Int. Med. Res.*, G. Micheal et al., **14**, 205 (1986). Hexamidine is preferably delivered as the diisethionate as Elestab HP 100® available ex Rhone-Poulenc; *inter alia*, as *RF 2535, Desomedine, Esomedine, Hexomedine, Ophtamedine.*

FORMULATIONS

For topical administration to the epidermis, the conjugates of the present invention may be formulated as ointments, creams, lotions, etc. which can be directly applied or delivered via an article of manufacture, *inter alia*, a diaper. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling

agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colorizing agents.

Typically the polymer conjugates of the present invention are formulated into a skin-compatible carrier which serves to solublized the conjugate in addition to providing a vehicle for uniform delivery of the enzyme inhibitor to the skin surface. The formulator of articles of manufacture which employ the enzyme inhibiting conjugates of the present invention will recognize the vehicle may take any form, *inter alia*, aqueous, non-aqueous, dry powder.

The amount of polymer conjugate which is present in the formulation depends upon the embodiment chosen by the formulator. In some instances, the polymer component of the conjugate itself may have properties which allow for the direct application of the conjugate without the need for a vehicle. However, when incorporated as part of a composition which comprises only polymer conjugate and a delivery vehicle, the conjugate will typically comprise from about 0.01%, preferably from about 1% to about 20%, preferably to about 10% by weight, of the delivery vehicle.

The compositions of the present invention will preferably comprise one or more adjunct ingredients which include carriers. For the purposes of the present invention the term "carriers" is used interchangeably with the term "emollients", "lotion base", etc. The formulator will recognize that certain carriers will have an emollient property or can serve more than one function. The compositions of the present invention comprise from about 1%, preferably from about 5%, more preferably from about 10% to about 99%, preferably to about 95%, more preferably to about 80%, most preferably to about 50% by weight, of one or more carriers. Non-limiting examples of carriers include petroleum-based emollients, sucrose ester fatty acids, polyethylene glycol and derivatives thereof, humectants, fatty acid ester type, alkyl ethoxylate type, fatty acid ester ethoxylates, fatty alcohol type, polysiloxane type, propylene glycol and derivatives thereof, glycerin and derivatives thereof, including glyceride, acetoglycerides, and ethoxylated glycerides of C_{12}-C_{22} fatty acids, triethylene glycol and derivatives thereof, spermaceti or other waxes, fatty acids, fatty alcohol ethers, propoxylated fatty alcohols, other fatty esters of polyhydroxy alcohols, lanolin, kaolin, any of the Federally monographed commercially available skin care. Suitable petroleum-based emollients include C_{16}-C_{32} hydrocarbons, including paraffins, include mineral oil and petrolatum (also known as "mineral wax", "petroleum jelly", and "mineral jelly").

The balance of the compositions of the present invention typically comprises, other than carriers, other adjunct ingredients. Non limiting examples of other preferred adjunct ingredients

include water, viscosity modifiers, perfumes, disinfectant antibacterial actives, antiviral agents, vitamins, pharmaceutical actives, film formers, deodorants, opacifiers, astringents, solvents, preservatives, viscosity modifiers, and mixtures thereof. In addition, stabilizers can be added to enhance the shelf life of the composition such as cellulose derivatives, proteins and lecithin

Water-based skin care carriers and compositions may optionally comprise a preservative, non-limiting examples or which include propyl paraben, methyl paraben, benzyl alcohol, benzalkonium, tribasic calcium phosphate, BHT, or acids such as citric, tartaric, maleic, lactic, malic, benzoic, salicylic, and mixtures thereof.

A preferred use of the polymer conjugates of the present invention is for treatment or prevention of skin irritation from exposure to human feces as it relates to diaper rash and other articles of manufacture used to contain human waste. The polymer conjugates of the present invention inhibit proteolytic and/or lipolytic enzymes whether endogenous or exogenous. Therefore the formulator can employ the conjugates of the present invention in any embodiment which has the purpose of modulating or prevent the effects of exposure to said enzymes. However, the formulations can have a variety of other uses, non-limiting examples of which include applying the compositions to cotton swabs wherein the compositions are applied to area where enzyme activity is to be inhibited or modulated (i.e., nasal canal, throat), applying the compositions to facial tissues or wipes for application to any skin surface or orifice, *inter alia*, nasal passage, ocular region.

The following are non-limiting examples of compositions according to the present invention:

A composition for inhibiting enzymes on human skin comprising:

a) from about 0.01%, preferably from about 0.5%, more preferably from about 1%, most preferably from about 1.5% to about 10%, preferably to about 7.5%, more preferably to about 5% by weight, of one or more polymer conjugates having the formula:

$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1; and

b) the balance carriers and adjunct ingredients.

A composition for application to human skin, said composition inhibiting proteolytic and/or lipolytic enzymes on human skin comprising:

a) from about 0.01%, preferably from about 0.5%, more preferably from about 1%, most preferably from about 1.5% to about 10%, preferably to about 7.5%, more preferably to about 5% by weight, of one or more polymer conjugates having the formula:

$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1;

b) from about 0.01%, preferably from about 0.05%, more preferably from about 0.1% to about 5%, preferably to about 2%, more preferably to about 1% by weight, of an adjunct biologically active ingredient, preferably hexamidine; and

c) the balance carriers and adjunct ingredients.

A composition for application to human skin, said composition inhibiting proteolytic and/or lipolytic enzymes on human skin comprising:

a) from about 0.01%, preferably from about 0.5%, more preferably from about 1%, most preferably from about 1.5% to about 10%, preferably to about 7.5%, more preferably to about 5% by weight, of one or more polymer conjugates having the formula:

$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1;

b) from about 0.01%, preferably from about 0.05%, more preferably from about 0.1% to about 5%, preferably to about 2%, more preferably to about 1% by weight, of hexamidine;

c) from about 0.01% by weight, of a carrier alcohol, preferably a C_{10}-C_{20} linear or branched, saturated or unsaturated alkyl alcohol;

d) from about 0.01% by weight, of a secondary benefit agent, preferably selected from the group consisting of vitamins, sun screens, depilatories, desiccants, astringents, and mixtures thereof;

e) from about 0.01% by weight, of an aesthetic, said aesthetic selected from the group consisting of perfumes, fragrances, dyes, colorants, and mixtures thereof; and

f) the balance carriers and emollients, said adjunct ingredients selected from the group consisting of petroleum-based emollients, sucrose ester fatty acids,

polyethylene glycol and derivatives thereof, humectants, fatty acid esters, alkyl ethoxylates, fatty acid ester ethoxylates, fatty alcohols, polysiloxanes, propylene glycol and derivatives thereof, glycerin, glyceride, acetoglycerides, and ethoxylated glycerides of C_{12}-C_{22} fatty acids, triethylene glycol and derivatives thereof, waxes, fatty acids, fatty alcohol ethers, propoxylated fatty alcohols, fatty esters of polyhydroxy alcohols, lanolin, kaolin, and mixtures thereof..

A composition for inhibiting enzymes on human skin comprising:

a) from about 0.01%, preferably from about 0.5%, more preferably from about 1%, most preferably from about 1.5% to about 10%, preferably to about 7.5%, more preferably to about 5% by weight, of one or more polymer conjugates having the formula:

$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1; and

b) the balance a delivery vehicle.

The following is an example of a composition comprising a polymer conjugate according to the present invention which is suitable for use in an absorbent article.

EXAMPLE 4

Ingredients	%
Petrolatum [1]	52.2
Stearyl alcohol [2]	36.9
Aloe [3]	0.9
Polymer conjugate [4]	10.0

1. White Protopet® available ex Witco.
2. CO 1897 available ex Procter & Gamble.
3. Veragel Lipid in Kaydol available ex Madis Botanicals.
4. Enzyme inhibitor according to Example 1.

The compositions of the present invention can also be delivered to skin via compositions which provide other primary benefits. The following disclose compositions which can incorporate the enzyme inhibiting polymer conjugates of the present invention and are each incorporated herein by reference.

Skin Cleansers

U.S. 5,641,479, Linares et al., issued June 24, 1997; U.S. 5,599,549, Wivell et al., issued February 4, 1997; U.S. 5,585,104, Ha et al., issued December 17, 1996; U.S. 5,540,852, Kefauver et al., issued July 30, 1996; and U.S. 5,510,050, Dunbar et al., issued April 23, 1996.

Facial Acne Preparations

U.S. 5,612,324, Guang Lin et al., issued March 18, 1997; U.S. 5,587,176, Warren et al., issued December 24, 1996; U.S. 5,549,888, Venkateswaran, issued August 27, 1996; and U.S. 5,470,884, Corless et al., issued November 28, 1995.

Shower gels

U.S. 5,650,384, Gordon et al., issued July 22, 1997; and U.S. 5,607,678, Moore et al., issued March 4, 1997.

Cosmetics

U.S. 5,641,493, Date et al., issued June 24, 1997; U.S. 5,605,894, Blank et al., issued February 25, 1997; U.S. 5,585,090, Yoshioka et al., issued December 17, 1996.

Hand, Face, and Body Lotions

U.S. 4,939,179, Cheney et al., issued July 3, 1990; and U.S. 5,607,980, McAtee et al., issued March 4, 1997.

Cosmetic and Cleansing Wipes

U.S. 4,045,364, Richter et al., issued August 30, 1977; European Patent Application, EP 0 619 074, Touchet et al., published October 12, 1994; U.S. Patent Number 4,975,217, Brown-Skrobot et al., issued December 4, 1990; U.S. 5,043,155, Puchalski et al., issued August 27, 1991; and U.S. 5,648,083, Blieszner et al., issued July 15, 1997.

METHOD OF USE

The present invention also comprises a method for the treatment and prevention of diaper rash and diaper dermatitis caused by the prolonged contact of human skin with body waste. The present invention also ameliorates and serves as a prophylactic means to prevent the occurrence of said skin irritation by providing a barrier against unwanted protease or lipolase enzymes.

The method of the present invention comprises the step of contacting human skin with a composition comprising:

a) an effective amount, preferably from about 0.1%, more preferably from about 1% by weight, of a polymer conjugate according to the present invention; and

b) the balance carriers and adjunct ingredients;

wherein said composition is optionally, but preferably, applied to a substrate, *inter alia*, diaper topsheet, sanitary napkin. The methods of the present invention are carried out a pH which is compatible with the skin of the user.

Preferably the methods of the present invention also include contacting human skin with an ingredient which provides an additional benefit to the user, *inter alia*, provides conditioning to the exposed skin.

Normally the methods of the present invention deliver an "effective amount" of the compositions, which is the minimum inhibitory concentration of the selected enzyme inhibitor, to the skin. However, depending upon the formulation and the means for performing the methods of the present invention, any amount may be delivered by the formulator.

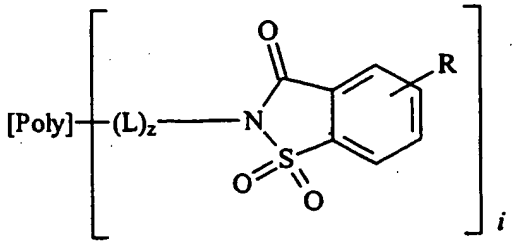
WHAT IS CLAIMED IS:

1. A polymer conjugate having the formula:

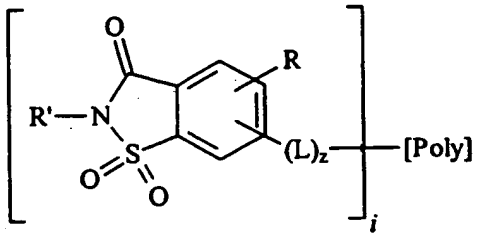
$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1.

2. A compound according to Claim 1 having a saccharin inhibitor component of the formula:



or the formula:



a) hydrogen;

b) C_1-C_{18} substituted or unsubstituted, linear or branched alkyl;

c) C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl

d) C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl;

e) C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl;

f) C_6-C_{18} substituted or unsubstituted aryl;

g) C_2-C_{18} substituted or unsubstituted heterocyclic alkyl;

h) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

i) alkylenearyl having the formula:

$$—(R^1)_n—R^2$$

wherein R^1 is C_1-C_{12} linear or branched alkylene, C_2-C_{12} linear or branched alkenylene, or mixtures thereof; R^2 C_6-C_{18} substituted or unsubstituted aryl, or mixtures thereof; n is from 1 to 16;

j) an amino unit having the formula:

$$—(CH_2)_mN(R^3)_2$$

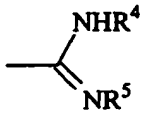
wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; m is from 0 to 10;

k) a quaternary ammonium unit having the formula:

$$—(CH_2)_m\overset{+}{N}(R^3)_3\ Y^-$$

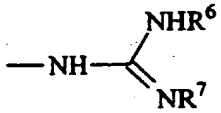
wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; Y is an anion of sufficient charge to provide electronic neutrality; m is from 0 to 10;

l) a unit having the formula:



wherein R^4 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^5 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^4 and R^5 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

m) a unit having the formula:



wherein R^6 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^7 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^6 and R^7 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

n) a unit having the formula:

$$—R^8—R^9$$

wherein R^8 is:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

iii) $-C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

iv) $-C(X)R^{11}C(X)-$, wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

v) $-C(X)NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vi) $-C(X)NR^{10}R^{11}NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vii) $-NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

viii) $-NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

ix) $-NR^{10}C(X)R^{11}NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

x) $-NR^{10}R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xi) $-NR^{10}C(X)R^{11}C(X)O-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xii) $-OC(X)R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiii) $-NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiv) $-R^{11}NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xv) $-R^{11}NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or

unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xvi) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

xvii) -O-;

xviii) $-(R^{11})_tC(X)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xix) $-(R^{11})_tOC(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xx) $-(R^{11})_tC(O)O(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxi) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is from 1 to 4;

xxii) -S-;

xxiii) $-(R^{11})_tS(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxiv) $-(R^{11})_tS(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxv) $-(R^{11})_tSO_2(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxvi) or mixtures thereof;

R^9 is:

i) hydrogen;

ii) C_1-C_{18} substituted or unsubstituted, linear or branched alkyl;

iii) C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl

iv) C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl;

v) C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl;

vi) C_6-C_{18} substituted or unsubstituted aryl;

vii) C_2-C_{18} substituted or unsubstituted heterocyclic alkyl;

viii) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

ix) -OH;

x) $-SO_3M$;

xi) $-OSO_3M$;

xii) $-NO_2$;

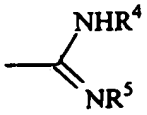
xiii) halogen selected from fluorine, chlorine, bromine, iodine, or mixtures thereof;

xiv) $-C(Hal)_3$, wherein each Hal is fluorine, chlorine, bromine, iodine, or mixtures thereof;

xv) $-COR^{14}$; wherein R^{14} is hydrogen, -OH, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, or mixtures thereof; $-N(R^{15})_2$, or mixtures thereof; each R^{15} is independently hydrogen, -OH, C_1-C_4 alkyl, or mixtures thereof;

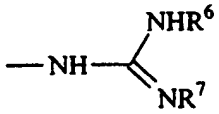
xvi) $-CH(OR^{14})_2$ wherein R^{14} is hydrogen, C_1-C_{12} alkyl, or two R^{14} units can be taken together to form a ring having from 3 to 5 carbon atoms; or mixtures thereof;

xvii) a unit having the formula:



wherein R^4 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^5 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^4 and R^5 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

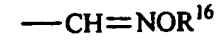
xviii) a unit having the formula:



wherein R^6 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^7 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^6 and R^7 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

xix) $-NHOR^{16}$, wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; acyl having the formula $-COR^{17}$, wherein R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xx) a unit having the formula:



wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; C_7-C_{22} linear or branched alkylenearyl; acyl having the formula $-COR^{17}$, R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xxi) an amino unit having the formula:

$$—(CH_2)_mN(R^3)_2$$

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; m is from 0 to 10;

xxii) a quaternary ammonium unit having the formula:

$$—(CH_2)_m\overset{+}{N}(R^3)_3\ Y^-$$

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; Y is an anion of sufficient charge to provide electronic neutrality; m is from 0 to 10;

o) two R units on the same carbon atom can be taken together to form a carbonyl unit or carbonyl unit equivalent; and

p) mixtures thereof;

L is a linking group; R' is R or a unit which serves to irreversibly bind said saccharin enzyme inhibitor component to a target enzyme, [Poly] is a polymeric unit, *i* indicates the number of said saccharin units which comprise said conjugate and has the value of from 1 to 100; z is 0 or 1.

3. A compound according to Claim 2 wherein R is:

a) hydrogen;

b) C_1-C_8 linear unsubstituted alkyl;

c) C_6-C_{10} unsubstituted cycloalkyl;

d) C_{10} and C_{15} branched alkenyl;

e) aryl units selected from the group consisting of phenyl, naphthyl, 4-methoxyphenyl, 4-nitrophenyl, 4-(C_1-C_4 alkyl)phenyl, and mixtures thereof;

f) C_4-C_6 substituted or unsubstituted heterocyclic alkyl;

g) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

h) alkylenearyl having the formula:

$$—CH_2—R^2$$

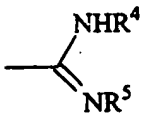
wherein R^2 is selected from the group consisting of phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, and mixtures thereof;

i) an amino unit having the formula:

$$—N(R^3)_2$$

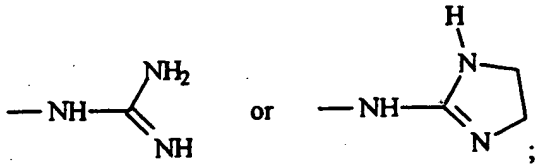
wherein each R^3 is independently hydrogen, methyl, ethyl, 2-hydroxyethyl, cyclopropyl, or mixtures thereof;

j) a unit having the formula:



wherein R^4 and R^5 are each hydrogen, or R^4 and R^5 is taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

k) a unit having the formula:



l) a unit having the formula:

$$—R^8—R^9$$

wherein R^8 is:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

iii) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

iv) -O-;

v) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is from 1 to 4;

vi) -S-;

vii) or mixtures thereof;

R^9 is:

i) an alkyl unit selected from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl;

ii) a cycloalkyl unit selected from cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 2,5-dimethylcyclopentyl;

iii) an aryl unit selected from phenyl, 4-methoxyphenyl, 4-nitrophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-aminobenzyl, 4-guanidiobenzyl;

iv) a heterocyclic unit selected from N-aziridinyl, 2-pyrrolindinyl, 3-pyrrolidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl;

v) -OH, when the index p is from 1 to 4;

vi) $-SO_3M$ when the index p is from 1 to 4;

vii) $-OSO_3M$ when the index p is from 2 to 4;

viii) $-NO_2$;

ix) chlorine, bromine, or mixtures thereof;

x) $-CF_3$;

xi) $-COR^{14}$; wherein R^{14} is -OH, $-NH_2$, $-N(CH_3)_2$, or mixtures thereof;

xii) $-NHOR^{16}$, wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; acyl having the formula $-COR^{17}$, wherein R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xiii) a unit having the formula:

$$—CH=NOR^{16}$$

wherein R^{16} is hydrogen or methyl; and

m) mixtures thereof.

4. A compound according to either of Claims 2 or 3 wherein R is:

a) hydrogen;

b) an alkyl unit selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, n-pentyl, isopentyl, n-hexyl, 2-methyl hexyl, 2-ethyl, hexyl, and mixtures thereof;

c) a cycloalkyl selected from the group consisting of cyclohexyl, 4-methylcyclohexyl, 4-isopropylcyclohexyl, and mixtures thereof;

d) a heterocyclic alkyl selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolindinyl, 3-pyrrolidinyl, 2-piperazinyl, N-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, N-morpholinyl, and mixtures thereof;

e) an amino unit selected from the group consisting of methylamino, dimethylamino, ethylamino, diethylamino, dicyclopropyl, and mixtures thereof;

f) a heterocycle selected from the group consisting of amidine, 2-pyridinyl, pyrimidinyl, imidazolyl, and mixtures thereof;

g) a unit having the formula:

$$—R^8–R^9$$

wherein R^8 is -O- and R^9 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, and mixtures thereof; and

h) mixtures thereof.

5. A compound according to any of Claims 2-4 wherein L has the formula:

$$—(R^{11})_h\{(X)_j[C(X)]_k(X)_j(R^{11})_h(X)_j[C(X)]_k(X)_j\}_f(R^{11})_h—$$

wherein R^{11} is C_1-C_{12} substituted or unsubstituted alkylene; C_2-C_{12} substituted or unsubstituted alkenylene; substituted or unsubstituted C_3-C_{12} cycloalkylene; substituted or unsubstituted aromatic; substituted or unsubstituted heterocyclic; X is oxygen, sulfur, NR^{10} wherein R^{10} is hydrogen, C_1-C_4 alkyl, phenyl, or R^{10} can be taken as part of a ring bonded to another moiety in the linking group, the indices h, j, and k are each independently 0 or 1, f is from 0 to 10.

6. A compound according to any of Claims 2-5 wherein said linking unit L is selected from the group consisting of:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

iii) $-C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

iv) $-C(X)R^{11}C(X)-$, wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

v) $-C(X)NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vi) $-C(X)NR^{10}R^{11}NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

vii) $-NR^{10}C(X)-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

viii) $-NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

ix) $-NR^{10}C(X)R^{11}NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

x) $-NR^{10}R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xi) $-NR^{10}C(X)R^{11}C(X)O-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xii) $-OC(X)R^{11}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiii) $-NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xiv) $-R^{11}NR^{10}C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xv) $-R^{11}NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xvi) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

xvii) -O-;

xviii) $-(R^{11})_tC(X)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1; wherein X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xix) $-(R^{11})_tOC(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xx) $-(R^{11})_tC(O)O(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxi) $-(R^{11})_tOC(O)O(R^{11})_t-$; wherein t is 0 or 1;

xxii) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is 1 or 2;

xxiii) -S-;

xxiv) $-(R^{11})_t S(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

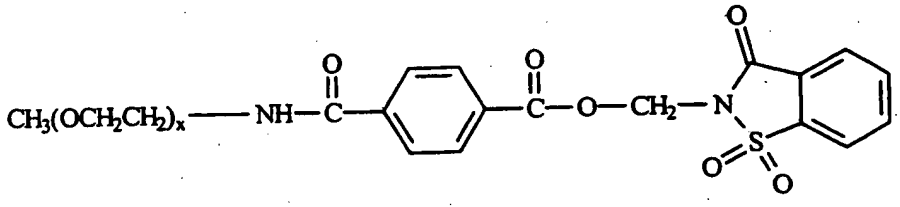
xxv) $-(R^{11})_t S(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxvi) $-(R^{11})_t SO_2(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxvii) or mixtures thereof.

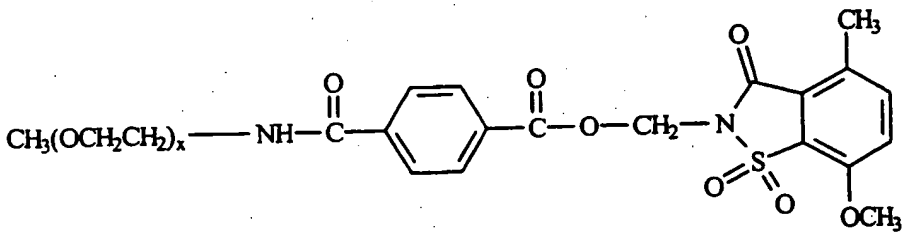
7. A compound according to any of Claims 2-6 wherein said [Poly] unit has a molecular weight of from 1000 daltons to 8,000 daltons.

8. A compound according to Claim 2 having the formula:



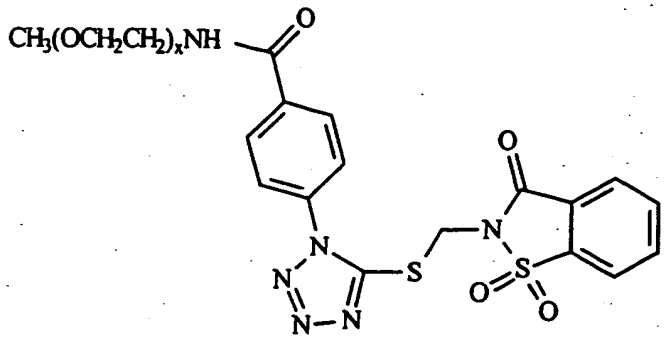
wherein x is from 50 to 250.

9. A compound according to Claim 2 having the formula:



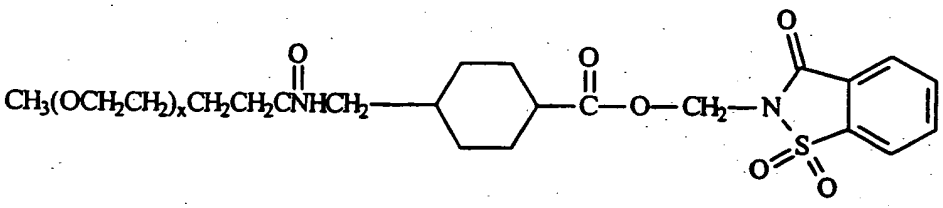
wherein x has a value such that the [Poly] unit has a molecular weight of 5000 daltons.

10. A compound according to Claim 2 having the formula:



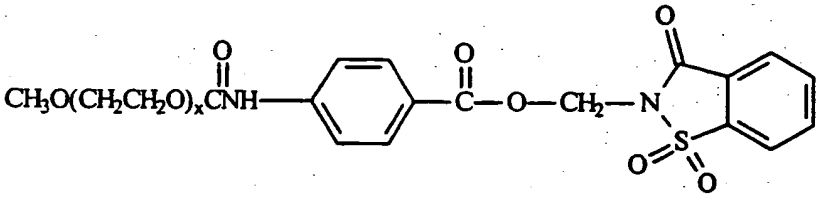
wherein x is from 50 to 250.

11. A compound according to Claim 2 having the formula:



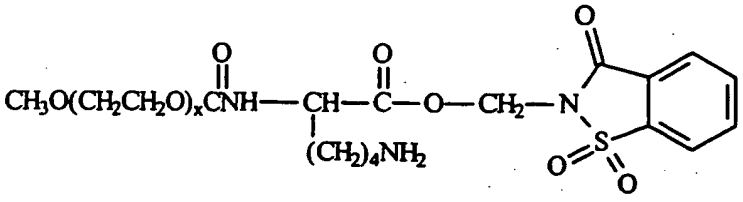
wherein x is from 50 to 250.

12. A compound according to Claim 2 having the formula:



wherein x is from 50 to 250.

13. A compound according to Claim 2 having the formula:



wherein x is from 50 to 250.

14. A composition for inhibiting enzymes comprising:

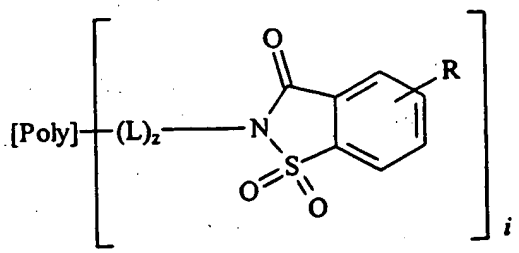
a) from 0.01% by weight, of one or more polymer conjugates having the formula:

$$T—(L)_z—[Poly]$$

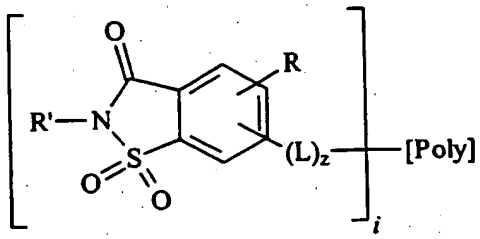
wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1; and

b) the balance carriers and adjunct ingredients.

15. A composition according to Claim 14 having a saccharin inhibitor component of the formula:



or the formula:



a) hydrogen;

b) C_1-C_{18} substituted or unsubstituted, linear or branched alkyl;

c) C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl

d) C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl;

e) C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl;

f) C_6-C_{18} substituted or unsubstituted aryl;

g) C_2-C_{18} substituted or unsubstituted heterocyclic alkyl;

h) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

i) alkylenearyl having the formula:

$$—(R^1)_n—R^2$$

wherein R^1 is C_1-C_{12} linear or branched alkylene, C_2-C_{12} linear or branched alkenylene, or mixtures thereof; R^2 C_6-C_{18} substituted or unsubstituted aryl, or mixtures thereof; n is from 1 to 16;

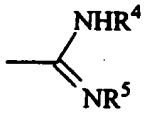
j) an amino unit having the formula:

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; m is from 0 to 10;

k) a quaternary ammonium unit having the formula:

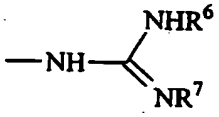
wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; Y is an anion of sufficient charge to provide electronic neutrality; m is from 0 to 10;

l) a unit having the formula:



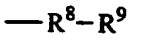
wherein R^4 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^5 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^4 and R^5 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

m) a unit having the formula:



wherein R^6 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^7 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^6 and R^7 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

n) a unit having the formula:



wherein R^8 is:

i) $-(CH_2)_p-$, wherein p is from 0 to 12;

ii) -C(O)-;

iii) $-C(X)NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

iv) $-C(X)R^{11}C(X)-$, wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

v) -C(X)NR[10]C(X)-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

vi) -C(X)NR[10]R[11]NR[10]C(X)-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

vii) -NR[10]C(X)-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

viii) -NR[10]C(X)NR[10]-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

ix) -NR[10]C(X)R[11]NR[10]-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

x) -NR[10]R[11]C(X)NR[10]-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

xi) -NR[10]C(X)R[11]C(X)O-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

xii) -OC(X)R[11]C(X)NR[10]-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

xiii) -NR[10]C(X)NR[10]R[11]-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR[10], and mixtures thereof;

xiv) -R[11]NR[10]C(X)NR[10]-, wherein R[10] is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R[11] is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; wherein X is oxygen, sulfur, NR[10], and mixtures thereof;

xv) $-R^{11}NR^{10}C(X)NR^{10}R^{11}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xvi) $-NR^{10}-$, wherein R^{10} is hydrogen, C_1-C_4 alkyl, or mixtures thereof;

xvii) -O-;

xviii) $-(R^{11})_tC(X)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1; X is oxygen, sulfur, NR^{10}, and mixtures thereof;

xix) $-(R^{11})_tOC(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xx) $-(R^{11})_tC(O)O(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxi) alkyleneoxyalkylene having the formula:

$$—(R^{12}O)_qR^{13}—$$

wherein R^{12} is C_2-C_6 linear or branched alkylene, substituted or unsubstituted phenylene; R^{13} is $-(CH_2)_p-$, wherein p is from 0 to 12; q is from 1 to 4;

xxii) -S-;

xxiii) $-(R^{11})_tS(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxiv) $-(R^{11})_tS(O)(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxv) $-(R^{11})_tSO_2(R^{11})_t-$; wherein R^{11} is C_1-C_{12} alkylene, substituted or unsubstituted phenylene, or mixtures thereof; t is 0 or 1;

xxvi) or mixtures thereof;

R^9 is:

i) hydrogen;

ii) C_1-C_{18} substituted or unsubstituted, linear or branched alkyl;

iii) C_3-C_{18} substituted or unsubstituted, linear or branched cycloalkyl

iv) C_2-C_{18} substituted or unsubstituted, linear or branched alkenyl;

v) C_2-C_{18} substituted or unsubstituted, linear or branched alkynyl;

vi) C_6-C_{18} substituted or unsubstituted aryl;

vii) C_2-C_{18} substituted or unsubstituted heterocyclic alkyl;

viii) C_3-C_{18} substituted or unsubstituted heterocyclic alkenyl;

ix) -OH;

x) $-SO_3M$;

xi) $-OSO_3M$;

xii) $-NO_2$;

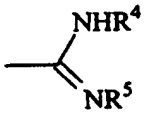
xiii) halogen selected from fluorine, chlorine, bromine, iodine, or mixtures thereof;

xiv) $-C(Hal)_3$, wherein each Hal is fluorine, chlorine, bromine, iodine, or mixtures thereof;

xv) $-COR^{14}$; wherein R^{14} is hydrogen, -OH, C_1-C_{12} alkyl, C_1-C_{12} alkoxy, or mixtures thereof; $-N(R^{15})_2$, or mixtures thereof; each R^{15} is independently hydrogen, -OH, C_1-C_4 alkyl, or mixtures thereof;

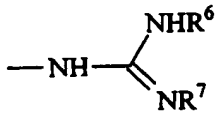
xvi) $-CH(OR^{14})_2$ wherein R^{14} is hydrogen, C_1-C_{12} alkyl, or two R^{14} units can be taken together to form a ring having from 3 to 5 carbon atoms; or mixtures thereof;

xvii) a unit having the formula:



wherein R^4 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^5 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^4 and R^5 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

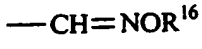
xviii) a unit having the formula:



wherein R^6 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^7 is hydrogen, C_1-C_4 alkyl, or mixtures thereof; R^6 and R^7 can be taken together to form a heterocyclic ring comprising from 3 to 5 carbon atoms;

xix) $-NHOR^{16}$, wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; acyl having the formula $-COR^{17}$, wherein R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xx) a unit having the formula:



wherein R^{16} is hydrogen; C_1-C_{12} linear or branched alkyl; C_7-C_{22} linear or branched alkylenearyl; acyl having the formula -COR^{17}, R^{17} is C_1-C_4 alkyl; or mixtures thereof;

xxi) an amino unit having the formula:

$$—(CH_2)_mN(R^3)_2$$

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; m is from 0 to 10;

xxii) a quaternary ammonium unit having the formula:

$$—(CH_2)_m\overset{+}{N}(R^3)_3\ Y^-$$

wherein each R^3 is independently C_1-C_{18} substituted or unsubstituted, linear or branched alkyl; Y is an anion of sufficient charge to provide electronic neutrality; m is from 0 to 10;

o) two R units on the same carbon atom can be taken together to form a carbonyl unit or carbonyl unit equivalent; and

p) mixtures thereof;

L is a linking group; R' is R or a unit which serves to irreversibly bind said saccharin enzyme inhibitor component to a target enzyme, [Poly] is a polymeric unit, *i* indicates the number of said saccharin units which comprise said conjugate and has the value of from 1 to 100; z is 0 or 1.

16. A composition for application to human skin, said composition comprising:

a) from 0.01% by weight, of one or more polymer conjugates unit which are capable of inhibiting one or more proteolytic enzymes having the formula:

$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1;

b) from 0.01% by weight, of an adjunct biologically active ingredient; and

c) the balance carriers and adjunct ingredients.

17. A method for preventing human skin irritation, said method comprising the step of contacting human skin with a composition comprising:

a) from 0.01% by weight, of one or more polymer conjugates capable of inhibiting one or more proteolytic enzymes having the formula:

$$T—(L)_z—[Poly]$$

wherein T is a saccharin ring-comprising enzyme inhibitor component, L is a linking unit, [Poly] is a polymer component, z is 0 or 1; and

b) the balance carriers and adjunct ingredients.

18. A method according to either Claim 16 or 17 wherein said adjunct ingredients are selected from the group consisting of petroleum-based emollients, sucrose ester fatty acids, polyethylene glycol and derivatives thereof, humectants, fatty acid esters, alkyl ethoxylates, fatty acid ester ethoxylates, fatty alcohols, polysiloxanes, propylene glycol and derivatives thereof, glycerin, glyceride, acetoglycerides, and ethoxylated glycerides of C_{12}-C_{22} fatty acids, triethylene glycol and derivatives thereof, waxes, fatty acids, fatty alcohol ethers, propoxylated fatty alcohols, fatty esters of polyhydroxy alcohols, lanolin, kaolin, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

Interna .al Application No
PCT/US 00/24714

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K7/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 594 257 A (STERLING WINTHROP INC) 27 April 1994 (1994-04-27) claims 1,14	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2001	05/02/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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